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UNITED STATES PATENT AND TRADEMARK OFFICE

BEFORE THE BOARD OF PATENT APPEALS
AND INTERFERENCES

Ex parte ANDREW PAUL CHAPMAN and DAVID JOHN KING

Appeal 2008-000454
Application 09/719,045
Technology Center 1600

Before TONI R. SCHEINER, LORA M. GREEN, and
RICHARD M. LEBOVITZ, *Administrative Patent Judges*.

LEBOVITZ, *Administrative Patent Judge*.

DECISION ON REMAND

BACKGROUND OF THE CASE

This case is on remand from the Federal Circuit. In a decision dated May 27, 2008 ("Decision"), the Board ("we") affirmed the Examiner's determination that claims 1-10 and 12-15 of the above-identified application were obvious in view of cited prior art that included the Gonzalez patent.[1] Appellants appealed the Board decision to the Federal Circuit. Upon review, the Federal Circuit found that the Board had made factual errors in reaching the decision to affirm the Examiner. *In re Chapman*, 595 F.3d 1330, 1339-40 (Fed. Cir. 2010). The court vacated the Decision and remanded the appeal to the Board for further proceedings. *Id.* at 1340. The court specifically told the Board, "[o]n remand . . . [the Board] need only revisit its conclusion of obviousness in light of a corrected understanding of Gonzalez." *Id.* The court further noted that the "Board is in no way precluded from, and indeed may be correct in, finding the claims to be obvious, particularly in light of Gonzalez's disclosure of joining two antibody fragments together with a polymer to make a dumbbell-shaped structure." *Id.*

The Federal Circuit held that we mischaracterized the disclosure at column 21, lines 50-59, of Gonzalez describing the structure of an $F(ab')_2$ antibody ("FF7" in the Decision) and incorrectly stated that there were three disclosed antibody fragments ("FF3" in the Decision), when "it is clear that . . . Gonzalez teaches different six possible antibody fragments." *Chapman*, 595 F.3d at 1339. In the new Findings of Fact section below, we have corrected these factual errors.

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[1] U.S. Pat. No. 6,025,158, issued February 15, 2000.

THE CLAIMS AND THE REJECTIONS

The claims are directed to a divalent antibody fragment comprised of two antibody heavy chains linked together by a polymer. The heavy chains are linked by "at least one non-disulphide interchain bridge linking the sulphur atom of a cysteine residue in one chain to the sulphur atom of a cysteine residue in the other chain." The polymer is recited in the claim as effective for increasing the circulating half-life of the antibody fragment.

Claims 1-10 and 12-15 were rejected by the Examiner as follows:

1) Claims 1-10, 12, 13, and 15 under 35 U.S.C. § 102(e) as anticipated by, or in the alternative, under 35 U.S.C. § 103(a) as obvious over Gonzalez (Ans. 4); and

2) Claims 1, 13, and 14 under 35 U.S.C. § 103(a) as obvious over Gonzalez and Barbanti (U.S. Pat. No. 5,436,154, July 25, 1995) (Ans. 6).

In the previous Decision, we reversed the anticipation rejection and therefore we do not address it any further.

Claims 1, 13, and 14 are representative and read as follows:

> 1. A divalent antibody fragment comprising two antibody heavy chains and at least one polymer molecule effective for increasing the circulating half-life of said fragment in covalent linkage, each heavy chain being covalently linked to the other by at least one non-disulphide interchain bridge linking the sulphur atom of a cysteine residue in one chain to the sulphur atom of a cysteine residue in the other chain, said cysteine residues being located outside of the variable region domain of each chain, characterised in that the at least one non-disulphide interchain bridge contains the at least one covalently linked polymer molecule.
>
> 13. An antibody fragment according to Claim 1 which is able to selectively bind to a cell surface or soluble antigen.

> 14. An antibody fragment according to Claim 13 wherein the antigen is human tumour necrosis factor-α or a platelet derived growth factor or a receptor thereof.

OBVIOUSNESS REJECTION OVER GONZALEZ

Claims 1-10, 12, 13, and 15 stand rejected under 35 U.S.C. § 103(a) as obvious over Gonzalez.

Findings of Fact ("rFF"[2])

rFF1. Gonzalez stated that its patent "relates to the field of antibody fragments derivatized with polymers, and in particular to the use of such derivatization to increase the circulation half-lives of antibody fragment-polymer conjugates." (Col. 1, ll. 13-16.) Polyethylene glycol (PEG) is described as an example of one such polymer (col. 1, ll. 2-42; col. 41, ll. 8-9; col. 27, ll. 12-14; Ans. 5).

rFF2. In the patent's Background section, Gonzalez acknowledged that PEGylation has not been shown to extend the half-life of antibodies in certain prior art references, but reported that "PEG attached to a sulfhydryl group in the hinge region of a Fab' fragment reduced clearance compared to the parental Fab' molecule." (Col. 1, ll. 30-43.)

rFF3. Gonzalez disclosed six possible antibody fragments: Fab, Fab', Fab'-SH, Fv, scFv, and $F(ab')_2$ (col. 21, ll. 33-41; *Chapman*, 595 F.3d at 1339).

rFF4. "Fab'-SH is the designation herein for Fab' in which the cysteine residue(s) of the constant domains bear a free thiol group." (Col. 11, ll. 62-64.)

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[2] The Findings of Fact in this Decision on Remand are abbreviated as "rFF" to distinguish them from the factual findings in the original decision.

rFF5. The conjugates described by Gonzalez "can be made using any suitable technique . . . for derivatizing antibody fragments with polymers. It will be appreciated that the invention is not limited to conjugates utilizing any particular type of linkage between an antibody fragment and a polymer" (col. 19, ll. 19-24; Ans. 5).

rFF6. In one embodiment, Gonzalez taught that the polymer can be targeted to the hinge region of the parental antibody fragment (col. 19, ll. 56-57). "The location of the hinge region varies according to the isotype of the parental antibody. Typically, the hinge region of IgG, IgD, and IgA isotype heavy chains is contained in a proline rich peptide sequence extending between C_H1 and C_H2 domains." (Col. 19, ll. 57-62.) The hinge region is in the constant domain of the antibody, outside the variable domain.

rFF7. Gonzalez taught an example of Fab'-S-PEG (cols. 120-123). In this example, Gonzalez described an SDS-Page gel showing a band "attributed to the heavy chain to which PEG is attached specifically at the hinge SH" of Fab' (col. 122, l. 64 to col. 123, l. 3; Ans. 5), a location which is outside the antibody variable region (rFF4).

rFF8. In another embodiment, Gonzalez described antibody conjugates in which "a polymer molecule is used to link together two antibody fragments to form a dumbbell-shaped structure. . . . Such structures can be made by using a polymer molecule derivatized with multiple functional groups permitting the direct attachment, or the attachment by means of bi- or multi-functional linkers, of two or more antibody fragments to the polymer backbone" (col. 35, ll. 45-57; at col. 41, ll. 41-43; *see* Ans. 5).

> rFF9.
>
> In yet another preferred embodiment, the conjugate contains a $F(ab')_2$ antibody fragment attached to no more than about 2 polymer molecules, wherein every polymer molecule is attached to a cysteine residue in the light or heavy chain of the antibody fragment that would ordinarily form the disulfide bridge linking the light and heavy chains, wherein the disulfide bridge is avoided by substituting another amino acid, such as serine, for the corresponding cysteine residue in the opposite chain.
>
> In a further embodiment, the conjugate contains an antibody fragment selected from the group consisting of Fab, Fab', and Fab'-SH, wherein the antibody fragment is attached to no more than 1 polymer molecule and the polymer is coupled to a cysteine residue in the light or heavy chain of the antibody fragment that would ordinarily form the disulfide bridge linking the light and heavy chains, wherein the disulfide bridge is avoided by substituting another amino acid, such as serine, for the corresponding cysteine residue in the opposite chain.

(Col. 21, l. 51 to col. 22, l. 2.)

Analysis

The Examiner bears the burden of establishing a prima facie case of unpatentability. *In re Oetiker*, 977 F.2d 1443, 1445 (Fed. Cir. 1992); *Ex parte Frye*, 94 USPQ2d 1072, 1075 (BPAI 2010). Here, the Examiner acknowledged there was no specific example in Gonzalez of an antibody having the claimed structure of two heavy chains covalently linked "by at least one non-disulphide interchain bridge linking the sulphur atom of a cysteine residue in one chain to the sulphur atom of a cysteine residue in the other chain." (Ans. 10-11.) However, based on teachings in the Gonzalez patent, the Examiner found that this structure would have been obvious to the ordinary skilled worker. The Examiner concluded:

> Appellant certainly cannot deny that there is an explicit teaching of how to conjugate an Fab'-SH fragment to derivatized PEG (col. 120, line 15-col. 122, line 31). The only step that one of ordinary skill in the art would need to take is to realize that, when a polymer molecule [is] used to link together two antibody fragments to form a dumbbell-shaped structure, such linkage to each of the two antibody fragments could be formed by the type of coupling chemistry shown at col. 120, line 15-col. 122, line 31" [which teaches PEG coupled to the hinge region of a cysteine residue of the heavy chain of Fab'].

(Ans. 15.)

Appellants contend that the Examiner erred. They assert that Gonzalez teaches away from the claimed antibody because Gonzalez "specifically discusses attaching polymer molecules to a cysteine residue on one chain of a divalent antibody fragment" and substituting the "corresponding cysteine residue in the opposite chain" with another amino acid (App. Br. 6; Reply Br. 5-6). Thus, Appellants argue that Gonzalez would have led persons of ordinary skill in the art away from the claimed antibody structure comprising an interchain bridge which links "the sulphur atom of a cysteine residue in one to the chain to the sulphur atom of a cysteine residue in the other chain." (App. Br. 7.)

The Examiner's determination that the claimed divalent antibody fragment would have been obvious to the ordinary skilled worker is supported by a preponderance of the evidence.

Gonzalez explicitly stated that antibody conjugates can be produced using any suitable technique and are not limited to "any particular type of linkage between an antibody fragment and a polymer" (rFF5; *see* Ans. 5). Thus, while Gonzalez described $F(ab')_2$ antibodies in which the polymer was linked to a cysteine residue on one chain (App. Br. 6; Reply Br. 5-6;

rFF9), we do not find that this "teaches away" from the claimed invention because Gonzalez expressly states that its conjugates are not limited to a particular linkage type (rFF5).

Gonzalez describes at least two distinct embodiments of divalent antibodies, the same type recited in claim 1. First, as noted by Appellants, Gonzalez described embodiments in which the polymer molecule was attached to one cysteine residue, while the other cysteine residue was substituted by another amino acid residue (App. Br. 6, citing col. 21, ll. 50-59; col. 23, l. 17 to col. 24, l. 27; and col. 31, l. 55 to col. 33, l. 2; rFF9). However, Gonzalez expressly described another antibody structure in which "a polymer molecule is used to link together two antibody fragments to form a dumbbell-shaped structure" (rFF8; *see* Ans. 5). This second antibody type is clearly an alternative to the first.

With respect to the latter dumbbell structure in which two antibody fragments are joined together, the issue is whether persons of skill in the art would have had reason to conjugate the fragments using a polymer molecule linked via a cysteine residue in each antibody heavy chain. Gonzalez did not explicitly teach utilizing the Fab'-SH fragment in the dumbbell-shaped structure. However, Gonzalez taught linking two antibody fragments together (rFF8). With six disclosed examples of antibody fragments (rFF3), there were only a limited number of fragments from which to choose to make the disclosed dumbbell-shaped structure. As all six were described, any one would have been the obvious choice, including the Fab'-SH fragment.

Upon choosing the Fab'-SH fragment, express preferences described in the Gonzalez patent would have led persons of ordinary skill in the art to

link the fragment, via its cysteine-SH group (rFF4), to the polymer molecule. In its Background section, Gonzalez referred to prior art which established that "PEG attached to a sulfhydryl group in the hinge region of a Fab' fragment reduced clearance compared to the parental Fab' molecule" (rFF2). The "sulfhydryl group" is a reference to the -SH present in a cysteine residue of the Fab' fragment. Gonzalez also disclosed the attachment of a polymer to the hinge region of its own invention (rFF6), and as pointed out by the Examiner, provided a complete working example in which the polymer PEG is coupled to the cysteine, via the -SH group, of the heavy chain hinge region (rFF7). Thus, persons of skill in the art would have recognized the advantages of attaching PEG to a cysteine residue at the hinge region and consequently would have been led to this configuration. The hinge region is in the antibody constant domain and thus "outside of the variable region domain" as required by claim 1.

We do not agree that the Examiner relied upon "'hindsight reconstruction to pick and choose among isolated structures'" (App. Br. 8). A dumbbell-shaped structure comprised of antibody fragments is specifically disclosed by Gonzalez (rFF8). The fact that a dumbbell is not the only structure disclosed in the Gonzalez patent does not disparage its use to construct a divalent antibody fragment.

Similarly, while Fab'-SH is among a list of six antibody fragments (rFF3 & rFF4), persons of ordinary skill would have been led to select Fab'-SH in making the dumbbell-shaped antibody for its recognized advantage when coupled to a PEG molecule (rFF2) and because Fab'-SH is used in a working example in the Gonzalez patent (rFF7). Both combined gave the skilled worker adequate reason to choose it.

Accordingly, we affirm the rejection of claim 1 as obvious over Gonzalez. Claims 2-10, 12, 13, and 15 fall with claim 1 because separate reasons for their patentability were not provided. *See* 37 C.F.R. § 41.37(c)(1)(vii).

REJECTION OVER GONZALEZ AND BARBANTI

Claims 1, 13, and 14 stand rejected under 35 U.S.C. § 103(a) as obvious over Gonzalez and Barbanti.

In *Chapman*, 595 F.3d at 1340, the Federal Circuit advised that "[o]n remand . . . [the Board] need only revisit its conclusion of obviousness in light of a corrected understanding of Gonzalez." In our Decision to affirm the rejection of claims 1, 13, and 14 over Gonzalez and the additionally cited Barbanti patent, we did not further rely upon the findings identified by the Federal Circuit in *Chapman* as factually incorrect. Consequently, it is unnecessary for us to reconsider our decision to affirm the Examiner's rejection of claims 1, 13, and 14 as obvious over Gonzalez in view of Barbanti.

NEW GROUND OF REJECTION

Because we have corrected certain factual errors in the record, we shall designate the rejection under 35 U.S.C. § 103 over Gonzalez as a new ground of rejection.

Regarding the affirmed rejection(s), 37 C.F.R. § 41.52(a)(1) provides "Appellant[s] may file a single request for rehearing within two months from the date of the original decision of the Board."

In addition to affirming the Examiner's rejection of one or more claims, this decision contains new grounds of rejection pursuant to 37 C.F.R.

§ 41.50(b) (effective Sept. 13, 2004, 69 Fed. Reg. 49960 (Aug. 12, 2004), 1286 Off. Gaz. Pat. Office 21 (Sept. 7, 2004)). 37 C.F.R. § 41.50(b) provides "new grounds of rejection pursuant to this paragraph shall not be considered final for judicial review."

37 C.F.R. § 41.50(b) also provides that the Appellants, WITHIN TWO MONTHS FROM THE DATE OF THE DECISION, must exercise one of the following two options with respect to the new grounds of rejection to avoid termination of the appeal as to the rejected claims:

> (1) Reopen prosecution. Submit an appropriate amendment of the claims so rejected or new evidence relating to the claims so rejected, or both, and have the matter reconsidered by the Examiner, in which event the proceeding will be remanded to the Examiner. . . .
>
> (2) Request rehearing. Request that the proceeding be reheard under § 41.52 by the Board upon the same record. . . .

Should the Appellants elect to prosecute further before the Examiner pursuant to 37 C.F.R. § 41.50(b)(1), in order to preserve the right to seek review under 35 U.S.C. §§ 141 or 145 with respect to the affirmed rejection, the effective date of the affirmance is deferred until conclusion of the prosecution before the Examiner unless, as a mere incident to the limited prosecution, the affirmed rejection is overcome.

If the Appellants elect prosecution before the Examiner and this does not result in allowance of the application, abandonment or a second appeal, this case should be returned to the Board of Patent Appeals and Interferences for final action on the affirmed rejections, including any timely request for rehearing thereof.

AFFIRMED; § 41.50(b)

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